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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/603,866	06/26/2000	Avi J Ashkenazi	P1761R1	2405

7590 10/27/2005

Genentech Inc
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EXAMINER	
KAUFMAN, CLAIRE M	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 10/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/603,866	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4-9,50-54 and 61-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4-9,50-54 and 61-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

Applicant's arguments filed 8/10/05 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 102

Claims 2, 4-10 and 50-53 remain rejected under 35 U.S.C. 102(b) as being anticipated by Wiley (Immunity, 1995) for the reasons set forth in the previous Office action.

Claims 2, 4-11 and 50-54 remain and new claims 61, 62, 64 and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,763,223 for the reasons set forth in the previous Office action and for the following reasons addressing new claims 61, 62, 64 and 65:

US 5,763,223 teaches recombinant expression vector pDC409 containing the cDNA encoding the full-length TRAIL receptor transformed into *E. coli* (col. 24, lines 6-15), and expression of TRAIL in prokaryotes such as *E. coli* with suitable expression vectors including pBR322 and pKK223-3 (col. 11, line 59, through col. 12, line 25). Expression of mammalian polypeptides in *E. coli* produces non-glycosylated polypeptides (col. 8, lines 62-64). The production is combined with the previously cited teachings of TRAIL purification of recombinantly produced active TRAIL in an aqueous buffer neutralized by the addition of Tris, pH 8 (col. 28, lines 66, through col. 29, line 2). A pharmaceutical composition is also provided comprising purified TRAIL, which may comprise buffers (paragraph beginning col. 18, line 58). Also taught is the TRAIL formulation in a lyophilized form (col. 19, lines 3-5).

Applicants argue that it was unexpected to find that Apo-2L forms trimers by way of a metal-binding site and the references relied upon by the Examiner do not teach or suggest an effective amount of zinc to stabilize Apo-2L trimers. Applicants urge that this metal-binding property could not have been appreciated and that the skilled artisan routinely used other means for stabilizing TNF ligand trimers. The argument has been fully considered, but is not

persuasive. The knowledge or appreciation of a metal-binding site necessary for Apo-2L trimer formation is not necessary for anticipation of the claimed invention. The anticipation of the claimed invention rests on the anticipation of the formulation by the above Wiley references which, it is maintained for the reasons of record, have an amount of zinc effective to stabilize the Apo-2 ligand trimers. As stated in the previous Office action (2/10/05):

> It is maintained that the buffer of Wiley more likely than not had zinc in amounts sufficient to cause stable trimers of Apo-2L. The reasons are several fold. First, Wiley used Tris, and as stated in the previous Office action (middle of page 4): "Tris also appears to be what Applicants used (p. 48, line 13) to reconstitute the purified Apo-2L and what was the contributor of metals, including zinc, shown in TABLE II." Second, there is nothing to suggest that the Tris used by Wiley is different in composition or purity compared to the Tris used by Applicants. Both are apparently from a commercial source and would be assumed to be of sufficiently equivalent purity for the purpose used. Third, it was appreciated at the time the Wiley reference was published that TNF ligands and, most likely, TRAIL ligands were most active as stable trimers. In the Wiley reference beginning in the last sentence of page 676 through the end of the paragraph it is stated: "The crystal structures of TNF and LTI are known and these ligands have been shown to fold into 9-pleated sheet sandwich structures and to form homotrimers.... These sequences in this region that are most conserved map to the stands that form these 9-pleated sheets, with the centrally located D strand having the greatest conservation. Therefore, it is like that TRAIL, like TNF, forms an oligomeric structure that is necessary to cross-link its cognate receptor, thereby transducing a signal to the target cell." On page 675, second to last sentence of first full paragraph, it also states, "Gel filtration analysis of the purified soluble TRAIL suggests that the native molecule is multimeric in solution...." In US Patent 5,763,223 (Wiley et al.), published before the effective filing date of the instant application, it is stated in col. 10, lines 61-65, "Certain members of the TNF family of proteins are believed to exist in trimeric form.... Thus, trimeric TRAIL may offer the advantage of enhanced biological activity." Fourth, something which is old does not become patentable upon the discovery of a new property. The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best* , 195 USPQ 430, 433 (CCPA 1977). With regard to the above rejections, the PTO does not have facilities for examining and comparing Applicants' claimed ligand/buffer formulation with the prior art's, and thus Applicants have the burden of persuasion to make some comparison between materials in order to establish unexpected properties for the claimed invention. Applicants can be required to prove that prior art products do not necessarily or inherently possess characteristics of the claimed Apo-2L formulation. *Ex parte Gray*, 10 USPQ2d 1922 (BPAI 1989) and *In re Best,* 195 USPQ 430, 433 (CCPA

1977). Currently, it appears that the formulation of Wiley does inherently have all the characteristics of the claimed invention. It is maintained that Applicants' finding that biologically active trimers of Apo-2L are stabilized by zinc is an unappreciated property that was, nevertheless, inherently present in the prior art formulation.

Applicants argue that the references do not describe particular aspects of the trimer form of Apo-2L or how a formulation can optimize stabilization of trimeric forms of the protein. The argument has been fully considered, but is not persuasive. No particular aspect(s) of the trimer structure is necessary for the claimed invention. The stabile formation of an Apo-2L trimer is required, and it is maintained for the reasons of record that the references teach the Apo-2L in a formulation that would inherently cause formation and stabilization of Apo-2L trimers, with all the limitations of the claims met intrinsically or extrinsically by the references.

NEW:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 63 is rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,763,223 and Pitti et al. (May 31, 1996, J. Biol. Chem., 271(22):12687-90, reference #76 cited by Applicants 12/26/00).

US 5,763,223 teaches soluble TRAIL (a.k.a. Apo-2L), with the sequence the same as amino acids 95-281 of SEQ ID NO:1 of the instant application, fused to FLAG®, as well as purification of recombinantly produced active TRAIL in an aqueous buffer neutralized by the

addition of Tris, pH 8 (col. 28, lines 66, through col. 29, line 2). Also taught is the recombinant expression vector pDC409 containing the cDNA encoding the full-length TRAIL receptor transformed into *E. coli* (col. 24, lines 6-15), and expression of TRAIL in prokaryotes such as *E. coli* with suitable expression vectors such as pBR322 and pKK223-3, and which can include selectable markers like antibiotic resistance gene (col. 11, line 59, through col. 12, line 25). Expression of TRAIL polypeptides in *E. coli* produces non-glycosylated polypeptides (col. 8, lines 62-64). Fusion proteins of TRAIL and FLAG® or His_{10} are taught for facilitating purification and identification of TRAIL, with subsequent cleavage to remove the epitope tag (col. 8, lines 30-54). It is noted that proteins capped with FLAG® "may also be resistant to intracellular degradation in *E. coli*" (col. 8, lines 42-44). A pharmaceutical composition is also provided comprising purified TRAIL, which may comprise buffers (paragraph beginning col. 18, line 58). Also taught is the TRAIL formulation in a lyophilized form (col. 19, lines 3-5). Soluble tagged TRAIL in trimers (EXAMPLE 7) and lysis of leukemia and lymphoma cells (EXAMPLE 9) was demonstrated. Additionally, soluble TRAIL also killed CMV virally infected cells (EXAMPLE 11). US 5,763,223 does not teach the formulation wherein the TRAIL ligand consists of amino acids 114-281.

Pitti et al. teach the full length TRAIL (Apo-2L) as well as a soluble TRAIL ligand consisting of amino acids 114-281 fused to a His_{10} sequence (p. 12689, col. 1, 3rd full paragraph). The soluble ligand was used to induce apoptosis in human tumor cell lines (TABLE I).

It would have been obvious to the artisan of ordinary skill in the art at the time the invention was made to produce the soluble ligand of Pitti et al. or US 5,768,233 in an unglycosylated form using *E. coli* for protein production and purification using Tris-containing aqueous buffer as taught by US 5,763,223, which methods were the well known and routine in the art. The production of soluble TRAIL as a FLAG® fusion protein would have had the recognized advantage of helping to prevent intracellular degradation in *E. coli* as taught by US 5,768,233. One would have been motivated to cleave the epitope tag after purification to avoid activity interference from the tag and to have a more accurate molecular weight measurement (see for example, col. 29, lines 3-13 of US 5,768,233, for the problem of maintaining the protein as a FLAG® fusion). It would have been obvious to use to *E. coli* for soluble TRAIL

production because it had the well known advantage of allowing use of a selectable marker to confirm proper vector integration of the desired cDNA and had the art-recognized qualities of reliable homogeneity of produced protein at adequate quantities. It would have been desirable to use a soluble TRAIL ligand, such as the one of Pitti et al., as a prospective cancer therapeutic or anti-viral agent since both US 5,763,223 and Pitti et al. showed that it can induce apoptosis in and kill cancer cells and US 5,763,223 showed that it could specifically kill viral cells. For these reasons, a formulation would have been obvious comprising unglycosylated soluble TRAIL consisting of amino acids 114-281 of SEQ ID NO:1 with an inherently effective amount of zinc due to its presence in Tris buffer to stabilize the TRAIL trimers in the formulation.

While US 5,763,223 is silent with respect to the presence and action of zinc in the formulation and its stabilization of a TRAIL trimer, it is maintained that it appears to be an inherent property of the formulation as supported by the following: Applicants formulated Apo-2L by addition of the purified Apo-2L to Tris, and state that "additional quantities of divalent metal ions were not added during fermentation or purification..." (p. 48, lines 11-13, of the specification). Applicants' TABLE II (p. 48) shows that Tris was the apparent contributor of metals, including zinc. Applicants' Apo-2L formulation appeared to comprised of what the TRAIL formulation of US 5,763,223 comprised. Therefore, the presence of zinc in an amount effective to stabilize TRAIL trimers is inherent to the formulation of US 5,763,223. Note that Applicants' information is not necessary to support the rejection under 35 USC 103 by US 5,763,223, but is only presented as supporting evidentiary information.

Applicants argue that that new claims 61-65 are not anticipated by the references because the Apo-2 ligand is non-glycosylated and in the case of claim 63, consist only of the recited soluble sequence not linked to a heterologous sequence. The argument has been fully considered, but is not persuasive. For the reasons discussed in the rejection under 35 USC 102 addressing the new claims and in the rejection under 35 USC 103 as set forth above, it is maintained that the new claims 61, 62, 64 and 65 are anticipated and claim 63 is obvious.

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. WO 97/25428 was cited by Applicants in the IDS filed 12/26/00. It shares an inventor with the instant application and teaches the full length Apo-2 ligand as well as a soluble Apo-2 ligand consisting of amino acids 114-281 fused to an epitope tag. It does not teach soluble Apo-2L without a heterologous sequence. The soluble ligand was used to induce apoptosis in human tumor cell lines. This reference is cumulative with the Pitti et al. reference relied upon above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (571) 272-0829.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Claire M. Kaufman, Ph.D.
Patent Examiner, Art Unit 1646
October 25, 2005

LORRAINE SPECTOR
PRIMARY EXAMINER